

## GI Manifestations of Food Allergies



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## Objectives

- Discuss GI cases related to various food disorders
- Distinguish between allergic and non-allergic food sensitivities
- Discuss gastrointestinal eosinophilia
- Review most common non-allergic food sensitivities
- Discuss how a gastroenterologist can use testing to define many of these disorders

## Allergies affecting the GI tract

- Many misconceptions among patients and physicians
  - Many people believe that they have food allergies and do not have them
  - Many physicians believe that keeping foods away from people, especially infants and young children will prevent allergies
- Much that is still not known about food allergies
  - Gluten insensitivity
  - FODMAP
- GI approach often different than ALLERGY

## Allergens

- Major allergenic foods PROTEINS (>85% of food allergy)<sup>1</sup>
  - Children: milk, egg, soy, wheat, peanut, tree nuts
  - Adults: peanut, tree nuts, shellfish, fish, fruits and vegetables
- Proteins or glycoproteins<sup>2</sup> (Almost always)
  - Generally heat resistant, acid stable
- Carbohydrate allergens (rare)
  - Recent report of adult-onset mammalian meat allergy triggered by galactose-alpha-1,3-galactose

<sup>1</sup>Sicherer SH, Sampson HA. Annu Rev Med 2009; 60:261-277.

<sup>2</sup>Chapman MD, et al. JACI 2007; 119(2):414-420.

<sup>3</sup>Commins SP, et al. JACI 2009;123:426-33

## Cutaneous Reactions

- Acute urticaria/angioedema (*allergic urticaria last minutes to hours, not days*)
- Chronic urticaria and angioedema > 6 weeks
- Food implicated in 1.4% of 554 adults with chronic urticaria (Champion R, et al, 1969)
- 31% of 226 had positive skin test(s) to food, but only 4% had symptoms confirmed by blinded food challenge (Volonakis M, et al, 1992)
- Contact urticaria
- Contact dermatitis (food handlers)
- Foods causing ECZEMA especially in infants



## Pollen-Food Syndrome (Oral Allergy Syndrome)



- Key foods: raw fruits and vegetables
- Clinical features:
  - rapid onset oral pruritus and mild angioedema
  - rarely progressive (2% have systemic reactions)
- Pathophysiology: pollen allergens are the primary sensitizers and homologous proteins in plant-derived foods elicit symptoms
- 30-70% of people with allergic rhinitis have oral allergy syndrome
- Degree of clinical reactivity may have seasonal variations

Ma S et al. JACI 2003;112:784-8.

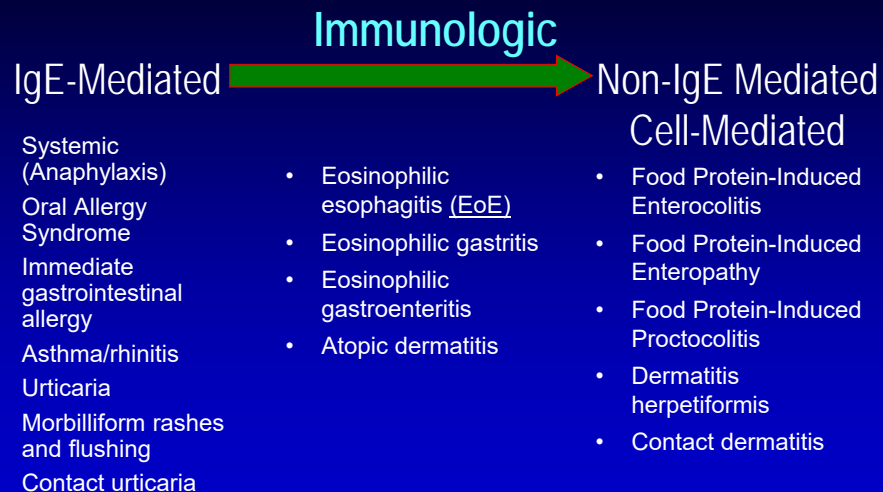
## Anaphylaxis

- Food allergy: #1 cause of anaphylaxis in the ED
- Incidence increased from average annual incidence 21/100,00 person-years in 1983-1987 to 49.8 /100,00 person-years in 1990-2010<sup>1</sup>
- Rapid-onset, 5-20% biphasic<sup>2</sup>
- May be localized (single organ) or generalized
- Potentially fatal
- Any food can induce anaphylaxis, but the majority of the most severe reactions triggered by peanut and tree nuts

<sup>1</sup>Decker et al, JACI 2008; 116:1-65.

<sup>2</sup>Lieberman P, Ann Allergy Asthma Immunol 2005;95:211-2.

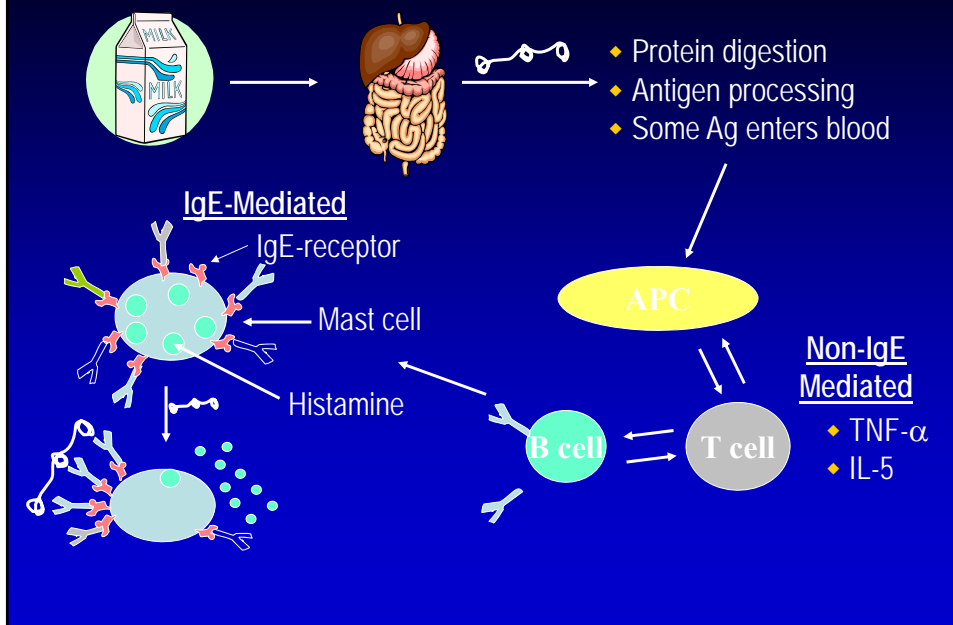
## Adverse Food Reactions



Sampson H. J Allergy Clin Immunol 2004;113:805-9.

Chapman J et al. Ann Allergy Asthma & Immunol 2006;96:S51-68.

## Immune Mechanisms of Food Allergy



## Categorization

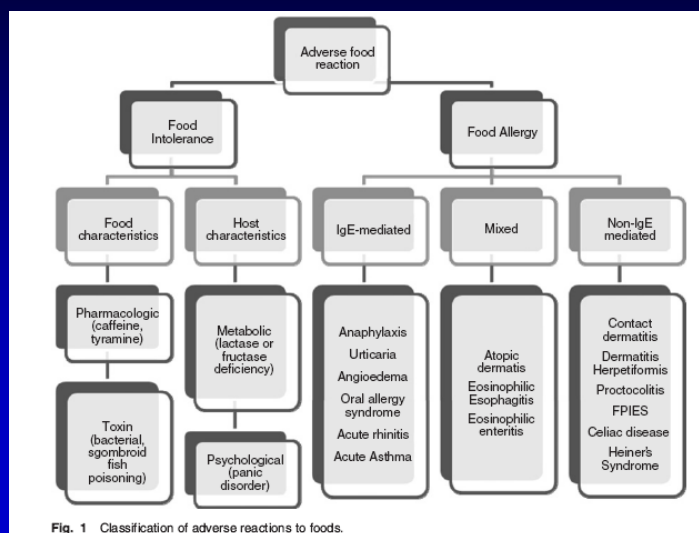


Fig. 1 Classification of adverse reactions to foods.

Cianferoni A and Spergel JM; *Allergy International* 2009; 58: 457-466.

## Case Presentation #1

- 2.5 month old infant with a 3 week history of blood streaked, frequent, loose stools
  - 5-7 bowel movements per day
  - Drinking formula (cow's milk) and breast feeding
  - Also has some vomiting
  - Also with streaks of mucus
  - No weight loss
  - Otherwise well appearing

**What else do you want to know ??**  
**Etiology?**

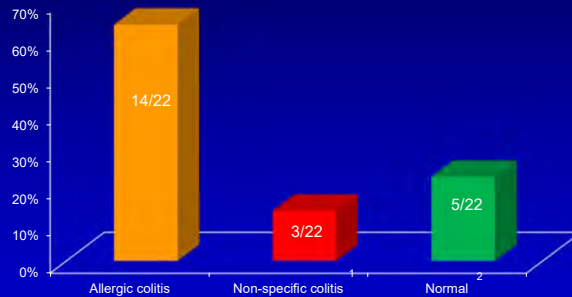


## Case #1

- Differential Diagnosis
  - Causes of Lower GI bleeding
    - Constipation – Fissures
    - Infections
    - Inflammatory bowel disease
  - Food allergy

## Bloody Stools in Healthy Infants Is It Always Allergic?

22 healthy infants (<6 mo) with rectal bleeding → Sigmoidoscopy



**36% of infants would have had diet unnecessarily changed  
Consider everything on differential diagnosis**

Xanthakos SA, et al; *J Pediatr Gastroenterol Nutr* 2005; 41:16-22

## Possible therapy if food allergy considered

- Don't change diet just for the sake of doing something — HAVE A PLAN
- Change maternal diet?
  - Stop breast feeding?
  - Empirically change formula to:
    - Soy?
    - Protein hydrolysate?
    - Elemental amino acid?
  - Perform tests?
    - What tests?
  - What to expect?

## Types of formulas

- Cow's milk formulas (with or without lactase)
  - Other additives (DHA, prebiotics, starch, etc)
- Soy based formula
  - Galactosemia, Hereditary Lactase deficiency, Vegan
- Protein hydrolysate
  - Classified "hypoallergenic"; predigested casein
  - ~ 50%-60% free amino acids; lactose free
    - Used for GI malabsorption; cow's milk/soy allergy
    - GI surgery; liver disease
- Elemental or Amino Acid based formulas
  - Free AA's, MCT, corn syrup solids, lactose free
  - True "hypoallergenic"
  - Severe allergies; eosinophilic GI; short gut; others

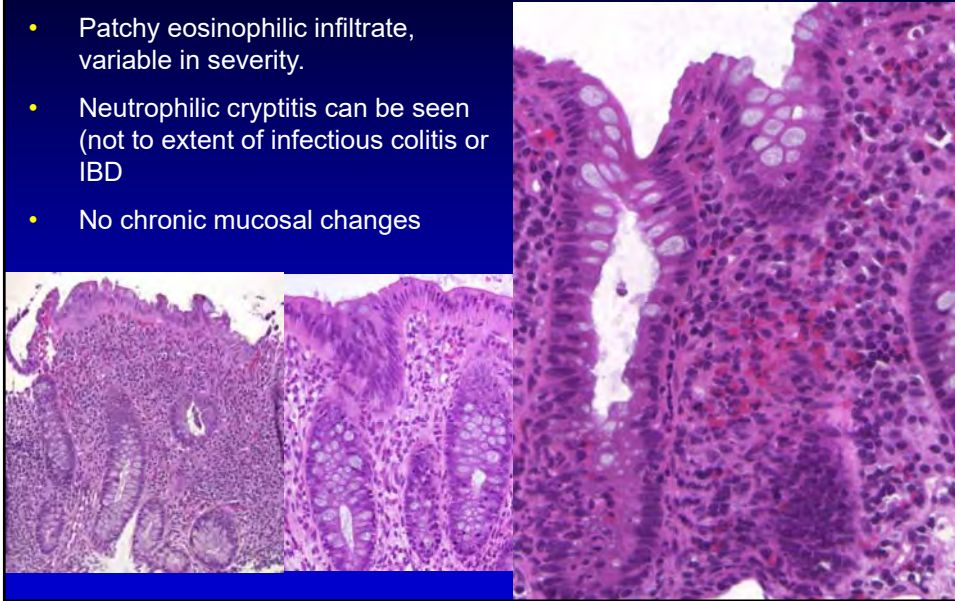
## Seen by Pediatric GI Specialist





## Allergic Proctocolitis

- Patchy eosinophilic infiltrate, variable in severity.
- Neutrophilic cryptitis can be seen (not to extent of infectious colitis or IBD)
- No chronic mucosal changes



## Allergic Proctocolitis

- 2-6% of infants in developed countries
- Usually cow's milk protein formula fed
  - 30% cross-reactivity with soy
  - >80% respond to protein hydrolysate formula
- Up to 60% breastfed
  - $\beta$ -lactoglobulin
  - Removal of dairy from mother's diet
  - Small percentage have to stop breastfeeding

Sampson HA, et al; *J Pediatr Gastroenterol Nutr* 2000; 30:S87-94

## Allergic Proctocolitis

### Clinical features

- Blood streaked stools
- Diarrhea
- Mucus in stool
- Normal weight gain
- Well-appearing
- Eczema, atopy - rare

### Laboratory features

- Can have a mild peripheral eosinophilia
- Can have an elevated serum IgE
- Rare
  - Hypoalbuminemia
  - Mild anemia

## Allergic Proctocolitis -- Treatment

- Formula fed
  - Protein hydrolysate (80% respond)
  - Amino acid formula if necessary
  - Soy formula (30%-60% cross-reactivity)
- Breastfed infants
  - Maternal dairy restriction
  - Infrequently other foods
  - Rarely need to stop breastfeeding
- 3-14 days: Improvement in clinic symptoms
  - Complete resolution of diarrhea, bleeding: Up to 4-6 weeks

## Cow's Milk Allergy

- Most likely cell-mediated or T-cell mediated disease
- Not IgE mediated – no anaphylaxis
- Almost always resolves
  - 12 mo? 18 mo? 24 mo? Sometimes longer?
- Food Reintroduction
  - First attempt at 12 months of age (NO DAIRY before)
  - First milk challenge in office (1 oz)
  - If tolerates – add slowly for next few weeks
  - If fully tolerates then can add cheese, yogurt, etc.
  - IF DOES NOT TOLERATE – (Retry 6 months later)
- Can RAST, skin prick testing help guide your decision?

## Case presentation #2

- 8 month old
  - Initially breastfed (except for formula first 3 weeks)
  - Solids introduced at 6 months (rice cereal, fruits, vegetables)
- Yogurt given for first time @ 8 months of age
  - 1 hour later: Irritability and severe vomiting
  - 2 hours later: Brought to Emergency Room limp, listless
  - Needed IV fluids
  - Sepsis infection - work-up negative
  - Returned to baseline after several hours of IVF and was discharged home 24 hours later doing well

## Case Presentation #2 (continued)

# FPIES

- Two days later → Older brother gave him yogurt again by accident
- Same symptoms but worse
- In Emergency Room, limp and ill-appearing
- Afebrile, HR 157 bpm, BP 63/45
- Treatment: subcutaneous epinephrine without improvement and IVF which helped
- No respiratory or skin problems
- **Diagnosis is...?**

## Food Protein Induced Enterocolitis Syndrome (FPIES)

- Different than Cow's milk allergy
- Onset: Typically 1<sup>st</sup> year of life
- Milk most common
  - 50% also react to soy
  - 33% will react to solids
- Multiple solid foods described
  - 80% react to >1 food protein
  - 60% also react to milk, soy
- Rarely happens from breast feeding
- Often needs an Amino acid based formula

## Food Protein Induced Enterocolitis (FPIES) – Clinical features

- Repetitive vomiting (~ 2 hours post ingestion)
- Diarrhea (~5 hours post ingestion)
  - Can have occult blood, WBCs
- Dehydration that may progress to:
  - Lethargy
  - Acidemia
  - Hypotension
  - Methemoglobinemia
- Occasional hypoalbuminemia and FTT



## FPIES Management

- IV fluid boluses
- Supportive care
- Epinephrine typically NOT helpful
- Avoidance



## Food Protein Induced Enterocolitis Syndrome (FPIES)

- Majority of patients become tolerant to inciting food by 3-5 years of age – able to fully reintroduce
- Not IgE mediated – T cell
- Diagnostic gold standard: Oral food challenge
- Oral food challenges required prior to food reintroduction – must be done in a hospital

Fogg MI, et al; *Pediatr Allergy Immunol* 2006; 17:351-355

## Allergic Proctocolitis (CMA) or FPIES

### CMA

- Diarrhea and mucus
- Blood streaked stools
- Normal weight gain
- Well-appearing
- Remove milk or soy
- Days to weeks to occur
- Usually resolves (age 1-2)
- Not life threatening
- Can challenge in office

### FPIES

- Severe abdominal pain
- Vomiting and Diarrhea
- Rapid onset
- Majority need immediate medical help
- Any food (dairy usually)
- If improves takes many years
- Can be life threatening
- Challenge in hospital

### Case #3

- 3 month old with severe irritability, and abdominal distention
- Stools 2-3 times a week, hard, no bleeding
- Occasional vomiting
- Poor weight gain
- Almost never happy, playful

### Case #3

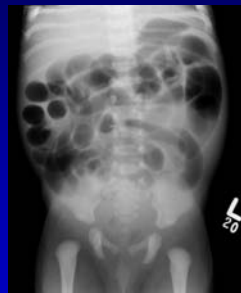
- Because of constipation and significant abdominal distention
  - Concern for an anatomic colonic problem

## Differential Diagnosis

- Constipation
- Hirschprung's disease
- Colonic stricture
- Malrotation/Volvulus
- Colitis
- Thyroid disease
- Allergy

## Tests performed

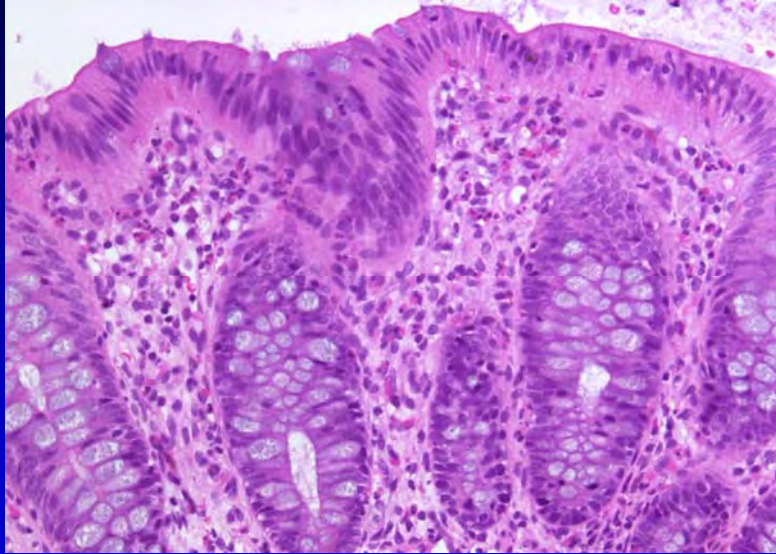
- Abdominal xray and unprepped barium enema
  - Abnormal in appearance



- Rectal suction performed - biopsy normal ganglion cells; however large number of eosinophils



## Allergic Proctocolitis



## Allergic Proctocolitis - Treatment

- Same treatment as Case 1

## Case #4

- 6 week old infant with severe irritability
- Always “crying for hours at a time”
- Parents report that the baby is “very gassy”
- Also infant has excessive “stomach gurgling”
- On cow’s milk formula
- Growing well, good weight gain
- No respiratory or skin problems
- At times very happy playful
- **What do you think?**

## Case #4

- Physical exam
  - Normal
- Labs
  - Blood count, chemistries – normal
  - Abdominal xray – normal

## Differential Diagnosis

- GI disease
  - Reflux, allergy, infections, malrotation, constipation, liver disease, etc
- Other system diseases
  - Renal disease, Central nervous system disease, Urinary tract infection, testicular torsion, metabolic disease
- Bone fracture, Child abuse
- Scratched cornea
- **NEED TO BE SURE NO OTHER ETIOLOGY**

## What is colic?

- Healthy infants - no other cause for symptoms
- Severe crying for at least 3 hours a day for 4 or more days a week
- Infants less than 4 months of age
- No clear etiology

## Red flags – Probably not colic

- Fever over 38.5 C
- Maternal drug use
- Poor weight gain, poor feeding
- Bilious vomiting
- Signs of physical abuse
- Recent head trauma
- Decreased activity or seizure

## Treatment of colic

- Behavior modification (Taubman)
- Use of simethicone (possible placebo)
- Describing colic to parents and explaining that it will improve
  - Rocking, swings (supervised)
  - Driving in car
  - Swaddling
- Most other medications **SHOULD NOT BE USED** – side effects

Peditrics 1984;74:998-1003

## Case Presentation #5

- 16 yo girl with intermittent abdominal pain, distention, and diarrhea
- Otherwise no problems – no bleeding, vomiting
- Possibly related eating specific foods
- Further questioning - ice cream, milk intake

## Lactose Breath Test

Figure 4: Double Peak

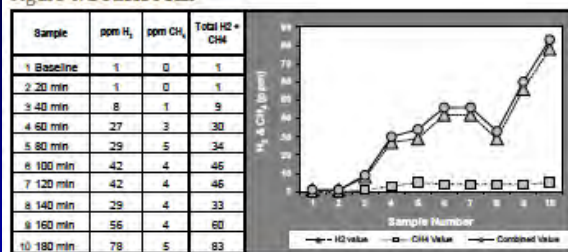
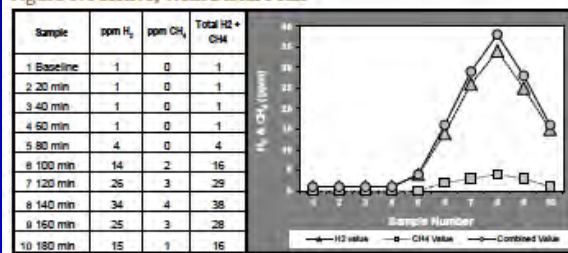
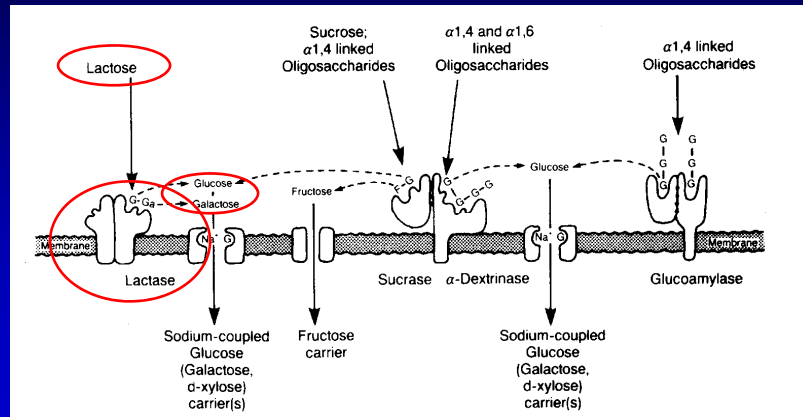


Figure 5: Positive, With Distal Peak



## Lactose Intolerance

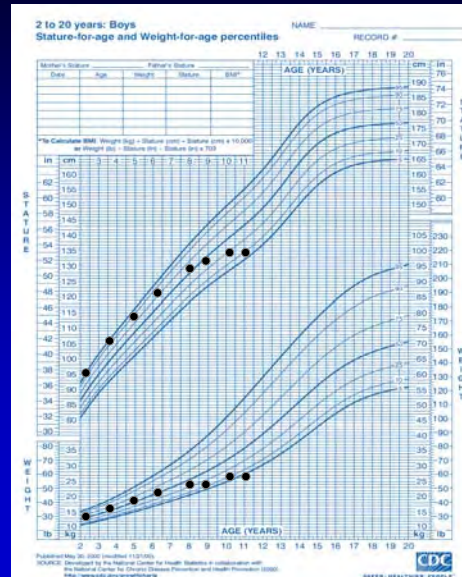


## Lactose Intolerance

- **Congenital Lactase Deficiency**
  - Extremely rare
  - Neonatal diarrhea and malabsorption
- **Primary Lactase Deficiency**
  - ~ 50-70% of population
  - African, Asian descent: 90-100%
  - Latin Americans ~ 50%
  - Decline in lactase levels starting after age 5
- **Secondary Lactase Deficiency**
  - Small bowel injury
  - Celiac disease, infection, Crohn's disease, radiation or drug induced enteritis



## Growth Curves – Very Helpful



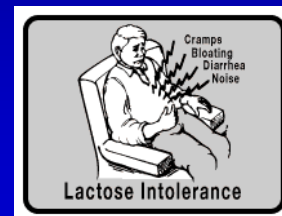
## Lactose Intolerance

### Diagnosis

- Hydrogen breath test
- Dietary trial
- Disaccharidase analysis (biopsy)

### Treatment

- Dietary modification
- Lactose free dairy products
- Lactase supplementation



## Lactose intolerance - Treatment

- Avoid Lactose containing foods
  - Not just dairy
- Use lactaid
- Make sure problem is not secondary lactose intolerance

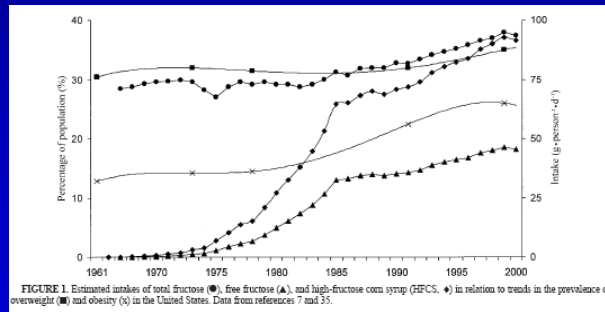
## What about other ingested sugars

- Fructose
- Sucrose



## Dietary Fructose

- Naturally occurring monosaccharide
  - Sucrose = Fructose + glucose
- Inexpensive sweetener
  - Sodas, fruit juices, candy
- Also found in many fruits



## Dietary Fructose Intolerance

- Most common symptoms: Distention, gassiness, diarrhea
- Children with isolated abdominal pain

### Diagnosis

- Hydrogen breath test
- Dietary trial

### Treatment

- Dietary modification



Gomara RE, et al; *J Pediatr Gastroenterol Nutr* 2008; 47:303-308  
Tsampalieros A et al; *Arch Dis Child* 2008; 93: 1078

## Dietary Fructose Intolerance

- Mechanism of intestinal absorption poorly understood
- Non-absorbed fructose
  - Osmotic load
  - Source for bacterial fermentation
- Intestinal fluid shifts
  - Distention
  - Bloating
  - Diarrhea



## FODMAP

- “Fermentable oligo-, di- and monosaccharides and polyols”
- Irritable bowel syndrome
- Many non-organic GI complaints

## Case #6

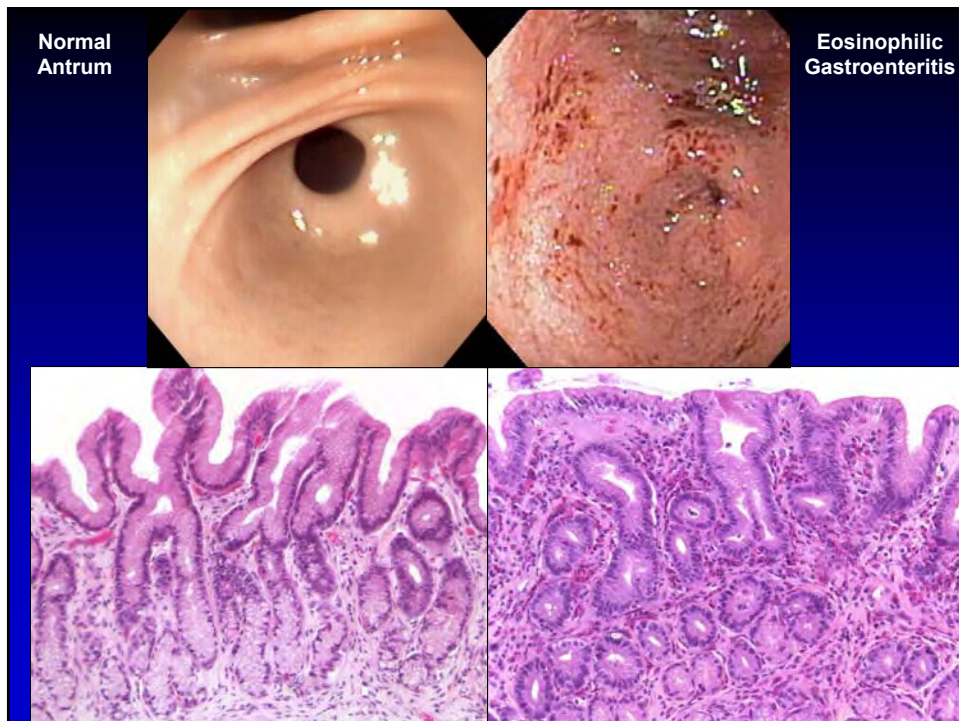
- 9 year old with 3 years of increasing severe abdominal pain, diarrhea, and vomiting
- Rare episodes of blood in vomitus
- Rare episodes of rectal bleeding
- Over last year lost 5-10 pounds
- History of asthma

## Case #6

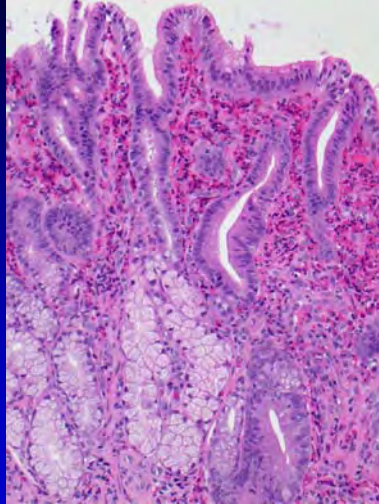
- Labs
- Complete Blood Count
  - Elevated white blood count
  - Elevated peripheral eosinophils
  - Decreased serum albumin

## Case #6

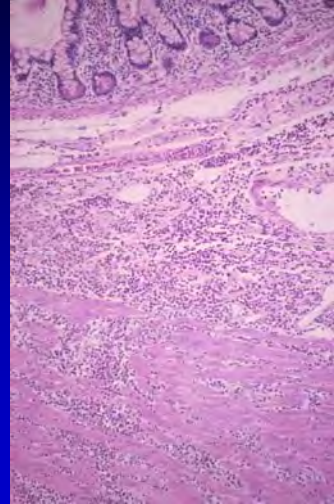
- Differential Diagnosis
  - Inflammatory Bowel disease – Crohn's disease
  - Autoimmune disease
  - Eosinophilic gastroenteritis
  - Other enteropathies



## Eosinophilic Gastroenteritis



Mucosal type



Mural type

## Eosinophilic Gastroenteritis

- Rare
- Eosinophilic infiltrate through GI tract
- GI symptoms
  - Vomiting, diarrhea, abdominal pain, protein losing enteropathy, obstruction
- Exclusion of known causes of GI eosinophilia
- Etiology unknown
  - Immunologic dysregulation
  - Food antigens
- Difficult to treat
  - Steroids
  - Dietary changes



## Eosinophilic Gastroenteritis

### Clinical characteristics

- Vomiting
- Severe abdominal pain
- Diarrhea, protein losing enteropathy
- Gastrointestinal bleeding
- Intestinal obstruction, perforation
- Peripheral eosinophilia, (50%?)
- Associated allergies: eczema, asthma, rhinitis, atopy

## Eosinophilic GI Disease

- Treatment
  - Diet
    - Restricted diet
    - Amino Acid based formula
  - Medications
    - Prednisone
    - Immunosuppressives
      - 6 mercaptopurine (6-MP)
      - Methotrexate
    - Biologics (future)
      - Anti IL-5

# Eosinophilic Gastroenteropathies

## The New Epidemic

Spectrum of disease or unique diseases?

Colon

Esophagus



Allergic proctocolitis

Eosinophilic esophagitis

Eosinophilic gastroenteritis

# Food Hypersensitivity Syndromes

IgE

Non-IgE

Immediate Hypersensitivity  
Oral Allergy Syndrome

Eosinophilic Esophagitis  
Eosinophilic Gastroenteritis

Food Protein Induced Enterocolitis  
Dietary Protein Enteropathy  
Dietary Protein Proctitis

## Case Presentation #7

- 7 year old girl presents with abdominal distention, mild abd pain
- Bowel pattern: 1 hard BM every 2-3 days
  - No withholding, high fiber diet
- Lost 4 lbs over the summer
- Parents report fatigue, fussiness
- Height at 10<sup>th</sup> percentile (previously 25-50%)
- Hb = 9.3, microcytic indices

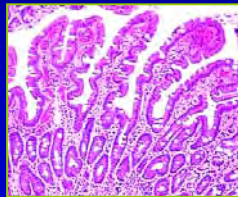
## Case #7 – Further testing

- ANTI-ENDOMYSIAL IgA: **Positive (1:160)**
- Ig A: **50**
- ANTI-TTG IgA: **133.9**
- Upper endoscopy: Duodenal biopsies consistent with **celiac disease**

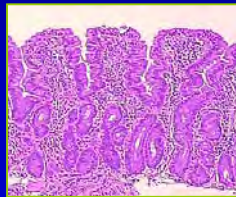


## Celiac disease – Histologic Diagnosis

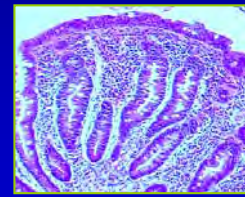
- Gold standard: Duodenal biopsies
  - Villous blunting, intraepithelial lymphocytosis



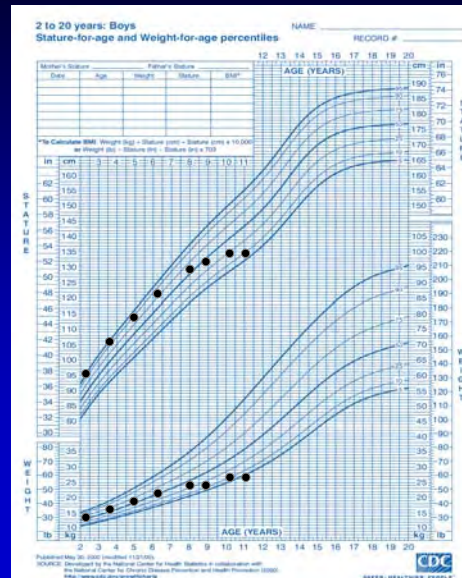
Normal

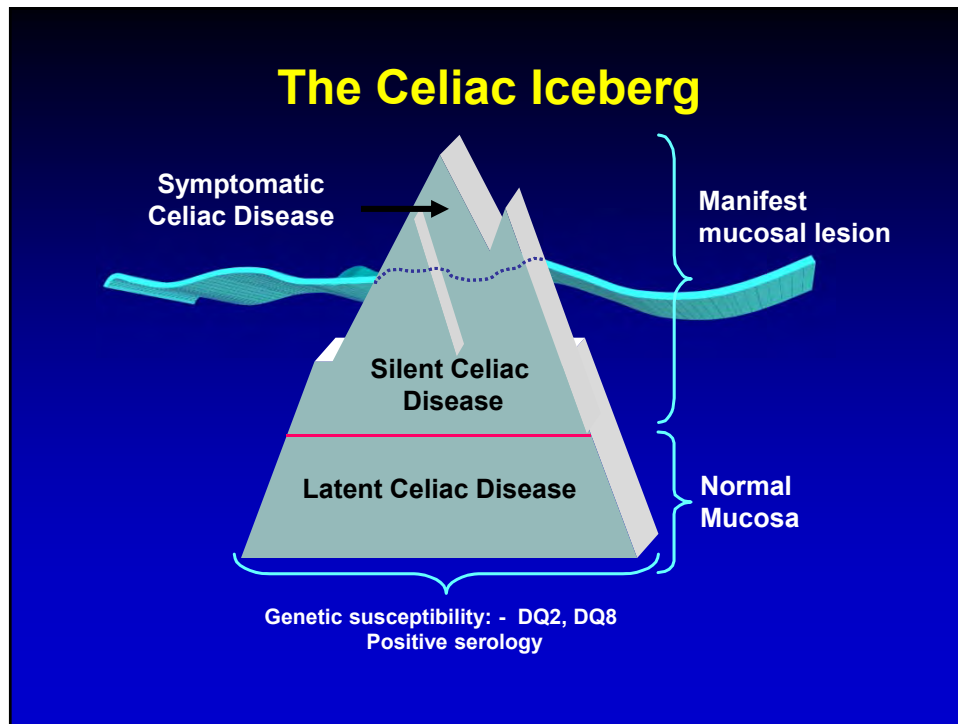


Partial atrophy



Total atrophy





## Celiac disease

- Immune-mediated enteropathy due to permanent sensitivity to gluten in genetically susceptible individuals
  - Wheat, rye, barley
- 1:133 incidence in United States
  - First degree relative: ~1:20
- Can present with or without gastrointestinal symptoms

## Celiac Gastrointestinal Manifestations (“Classic”)

- Chronic or recurrent diarrhea
- Abdominal distention
- Anorexia
- FTT/loss of weight
- Abdominal pain
- Vomiting
- Constipation
- Irritability

## Celiac disease – Non Gastrointestinal Manifestations

**Most common age of presentation: older child to adult**

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

## Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
TTG (IgA)	90 – 98	94 – 97

Serum IgA must be normal to properly interpret

Farrell RJ, and Kelly CP. *Am J Gastroenterol* 2001;96:3237-46.

## HLA Testing

- HLA-DQ2 or HLA-DQ8
- Useful in helping to identify disease when biopsies or serum markers inconclusive
- If both are negative very unlikely that celiac disease is present

## Celiac Disease – Treatment



- Only treatment for celiac disease is a gluten-free diet (GFD)
- Strict, lifelong diet
- Avoid:
  - Wheat
  - Rye
  - Barley

## Case 8

- 3 yo with poor weight gain and feeding difficulty
- 5 yo with intermittent vomiting and epigastric pain
- 8 yo with frequent regurgitation and heartburn that recurs after stopping a PPI
- 12 year old with complaints of “difficulty swallowing”
- 15 year with an “emergent” esophageal food impaction requiring immediate removal
- 28 year old with chronic heartburn and nausea
- 36 year old requiring emergent endoscopy for an esophageal food impaction

## EoE

- Food allergy that needs joint GI & Allergy involvement

## Conclusions

- Food allergies and Food Intolerances are being seen by both pediatric and adult gastroenterologists in increasing numbers
- Instead of guessing the cause of disease, testing exists to help identify many of these problems
- Gastroenterologists and allergists can be useful partners to determine accurate diagnosis of many of these disorders